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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Francisco, Joseph A. et al.

U.S. Serial No: 09/724,406

Filing Date: November 28, 2000

Title: *RECOMBINANT ANTI-CD30 ANTIBODIES AND USES THEREOF*

Commissioner for Patents
Washington, D.C. 20231

DECLARATION BY DR. ROBERT F. GRAZIANO UNDER 37 CFR 1.132 IN SUPPORT OF PUBLIC PROTEST AGAINST US SERIAL NO. 09/724,406

I, Dr. Robert Graziano, declare that:

1. I am presently Senior Director of Product Development at Medarex, Inc. in Bloomsbury, New Jersey. I received a B.S. in Biology from Allegheny College in 1978, and a Ph.D. in Biochemistry from Dartmouth College in 1988. My CV is attached hereto as Schedule 1.

2. I understand that the claims filed in the above-referenced US Patent Application Serial No: 09/724,406 are directed to (i) methods for treating or preventing Hodgkin's Disease in a subject by administering an antibody in a pharmaceutically acceptable carrier that immunospecifically binds CD30 and exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line, and (ii) to pharmaceutical compositions containing an antibody, which is not AC10 or HeFi-1 nor results from cleavage of AC10 or HeFi-1 with papain or pepsin, in a pharmaceutically acceptable carrier, wherein the antibody immunospecifically binds CD30 and exerts a cytostatic or cytotoxic effect on a Hodgkin's Disease cell line.

3. I am making this declaration to provide evidence that the claims in the above-referenced patent application are not patentable for lack of novelty based on the studies and prior art anti-CD30 antibodies described by Pohl et al., 1993, Int. J. Cancer 54:418-425 and Falini et al., 1992, Brit. J. Haematology 82: 38-45. I am also making this declaration to provide evidence that the claims in the above-referenced application are not patentable for lack of enablement.

4. Specifically, I conducted the following *in vitro* studies using an anti-CD30 antbody, referred to as HRS-4 (also referred to as Ab1), described by Pohl et al., which showed that this antibody possesses the claimed property of exerting a cytostatic effect on HD cells, as measured in the same cytotostatic cross-linking assay described in the application. In addition, the studies performed by Pohl et al. showed that HRS-4 exerts a cytotoxic effect on HD cells, as measured in the same cytotoxicity complement-mediated assay described in the application, and can be used *in vivo* to treat Hodgkin's Disease in animal models. Thus, the data described herein clearly demonstrates that the studies described by Pohl et al. using HRS-4 anticipate every element of the claimed invention.

In addition, I tested an anti-CD30 antibody, referred to as Ber-H2, described by Falini et al., in the same *in vitro* assay as HRS-4, which showed that this antibody also exerts a cytostatic effect on HD cells. However, contrary to the properties of HRS-4 described by Pohl et al., the studies performed by Falini et al. demonstrated that Ber-H2 does not treat Hodgkin's Disease *in vivo* (in patients). Thus, the data provided herein shows a lack of correlation between the claimed property of exerting a cytostatic or cytotoxic effect on HD cells and the claimed property of being useful for *in vivo* treatment of Hodgkin's disease. As such, the claimed invention in my opinion is not enabled since the application fails to provide any guidance for selecting anti-CD30 antibodies having the claimed therapeutic property of treating Hodgkin's disease and, thus, would require undue experimentation to make and use the invention as claimed.

5. The studies that I performed to generate the aforementioned data were conducted using antibodies Ber-H2, HRS-4 and a third prior art anti-CD30 antibody (as a control), referred to as AC-10. I tested these antibodies for their ability to inhibit growth of CD30, using a goat anti-mouse cross-linking antibody, in the following cell lines: L540 (Hodgkin's lymphoma derived cell line with a T cell phenotype), L428 (Hodgkin's lymphoma derived cell line with a B cell phenotype) and Karpas 299 (anaplastic large cell lymphoma derived tumor line). I employed a Ramos cell line (CD30 negative lymphoma) and the anti-murine cross-linking antibody alone in control experiments to confirm binding specificity and growth inhibition of the anti-CD30 antibodies.

6. I cultured the cell lines in flat-bottomed, 96-well tissue culture plates in a final volume of 200 µl/well (in triplicate), and added the anti-CD30 antibodies to the cell lines to a final concentration of 2 µg/ml and the secondary cross-linking antibody to a final concentration

of 8 μg/ml. After 96 hours, I pulsed the plates with ^{3}H-thymidine (0.5 μCi/well) and incubated for an additional four hours before harvesting and counting on a scintillation counter.

7. The result of this experiment was that all of the anti-CD30 antibodies inhibited growth of the CD30-expressing L540 cells (Figure 1A), L428 cells (Figure 1B), and Karpas 299 cells (Figure 1C) when cross-linked with the secondary antibody, as shown by a decreased uptake of ^{3}H-thymidine. The cross-linking goat anti-mouse antibody alone did not mediate this growth inhibition. Growth of the CD30 negative lymphoma line, Ramos, was not affected by any of the treatments (Figure 1D). These data demonstrate that the prior art antibodies HRS-4 and Ber-H2 can exert cytostatic or cytotoxic effects on HD cell lines *in vitro*, similarly to the antibodies claimed.

8. I understand that any willful false statements made in this declaration are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the accompanying public protest. I declare that all of the foregoing statements made of my own knowledge are true and that all statements made on information and belief are believed by me to be true.

Dated: 4/16/04

Signed: Robert F. Graziano
Robert Graziano, Ph.D.

Figure 1A - L540 Cells

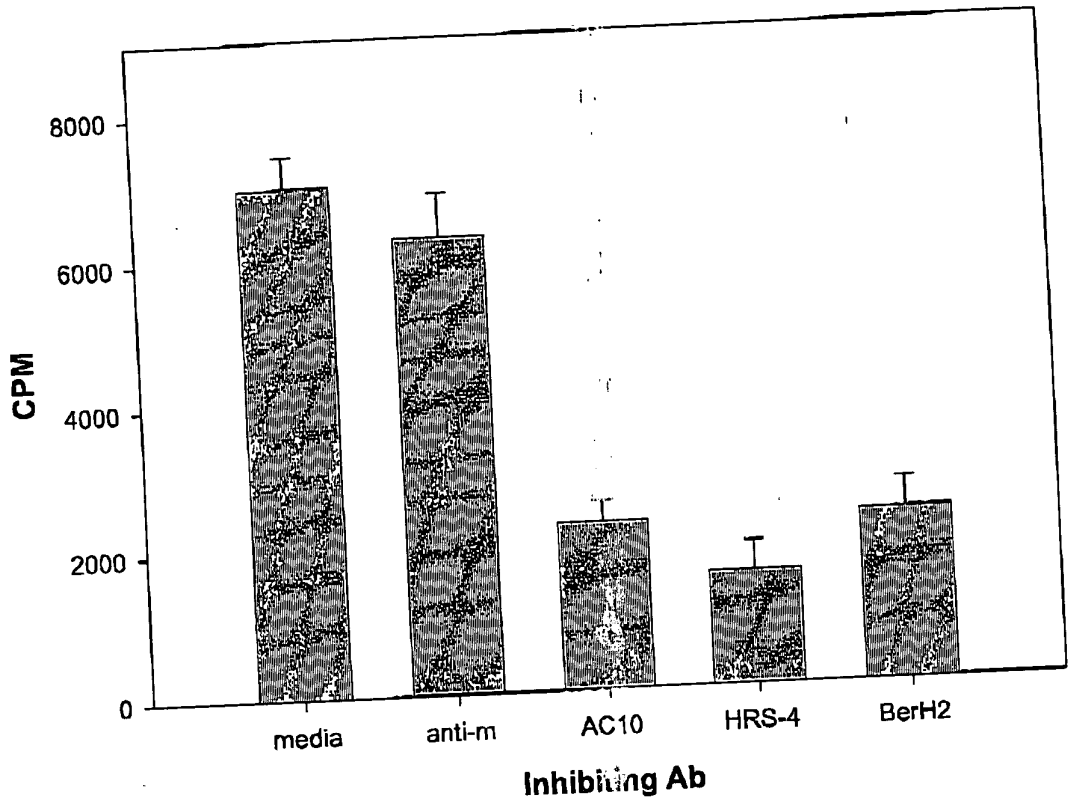


Figure 1B - L428 Cells

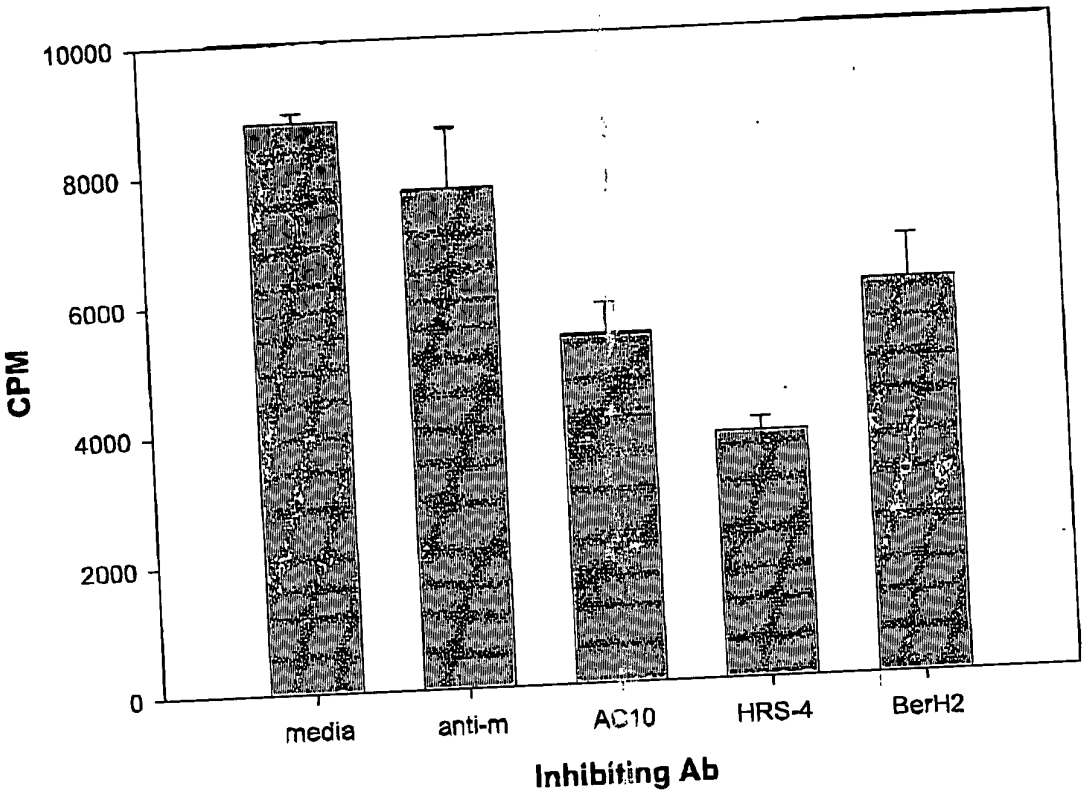


Figure 1C - Karpas 299 Cells

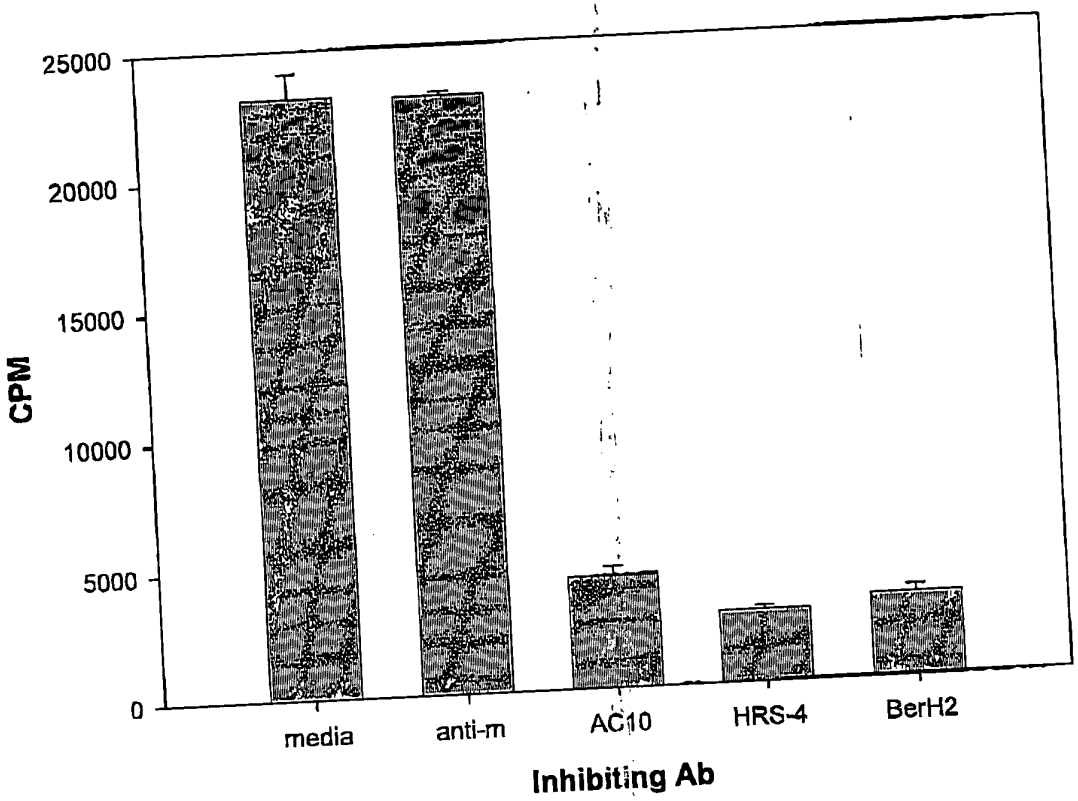
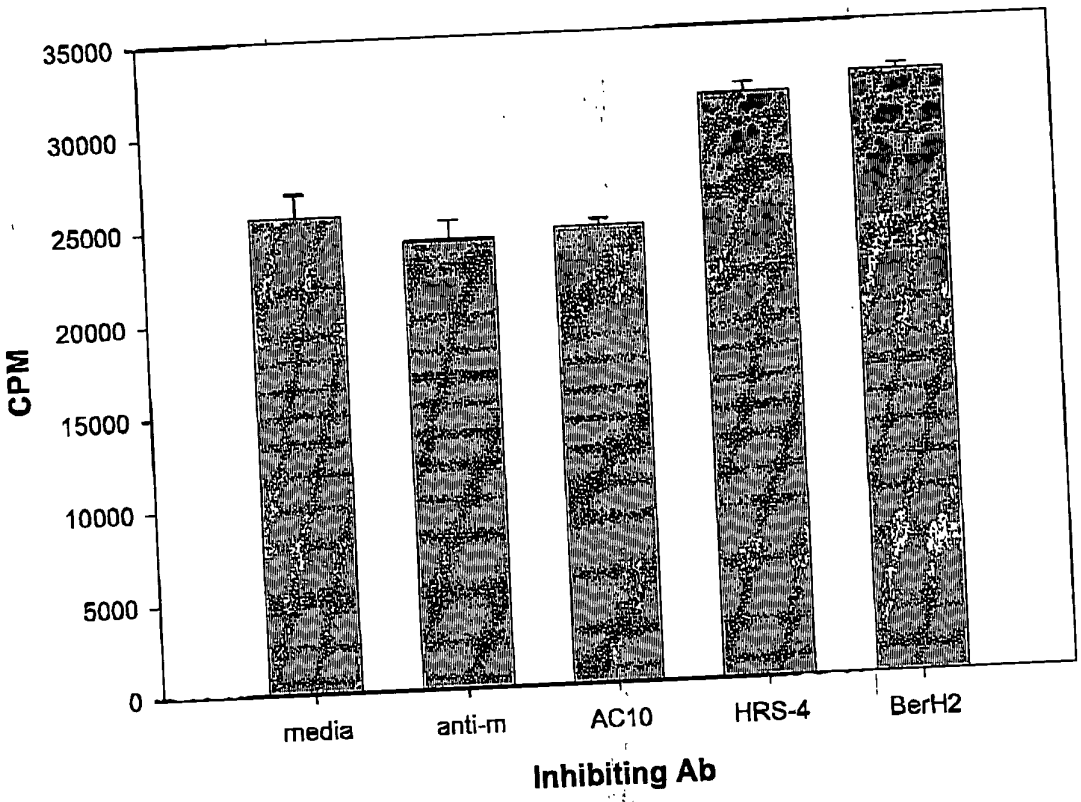


Figure 1D - Ramos Cells



Schedule 1

CV for Robert F. Graziano, Ph.D.

PROFESSIONAL EXPERIENCE

Senior Director of Product Development 2002-present
Director of Product Development 2001-2002
Medarex, Inc., 519 Route 173 West, Bloomsbury, NJ 08804

- Manage a team of scientists including molecular and cell biologists
- Initiate and manage collaborations with companies and academic institutions
- Create, characterize, and develop antibody-based therapeutics for treatment of cancer, autoimmune diseases, or infectious diseases utilizing Medarex's proprietary HuMAb mouse® technology
- Manage a molecular biology group responsible for support functions for Medarex, including cloning and sequencing antibody V region genes from hybridomas
- Responsible for an intermediate-scale antibody production and purification group

Associate Director of Research and Development 1998-2001
Assistant Director of Research and Development 1996-1998
Medarex, Inc., 1545 Route 22 East, Annandale, NJ 08801

- Supervised a staff of 10 scientists
- Responsible for developing and characterizing novel bispecific antibodies
- Responsible for developing novel fusion proteins that target the human Fc receptors CD64 and CD89 in order to mediate direct tumor killing or for the development of tumor vaccines

Principal Scientist 1993-1996
Medarex, Inc., 1545 Route 22 East, Annandale, NJ 08801

- Responsible for the construction and characterization of chemically-linked bispecific antibodies
- Provided support for assay development, quality control, and production groups

Senior Staff Scientist 1992-1993
Medarex, Inc., 12 Commerce Ave., West Lebanon, NH

- Responsible for developing R&D efforts for the company
- Responsible for the development and clinical production of the first lot of MDX-210, a chemically-linked bispecific antibody

Adjunct Assistant Professor 1992-1993
Dartmouth Medical School, Department of Microbiology, Lebanon, NH

Research Assistant 1981-1984
Dartmouth Medical School, Department of Microbiology, Hanover, NH

- Generated monoclonal antibodies to cell surface receptors on human leukocytes

Research Assistant 1979-1981
Case Western Reserve University, Department of Microbiology, Cleveland, OH

EDUCATION

1989-1992

Postdoctoral Research Associate
Washington University School of Medicine, Department of Pathology, St. Louis, MO
- Generated and characterized murine T cell hybridomas specific for HIV-encoded proteins

1988-1989

Postdoctoral Research Associate
Dartmouth College, Department of Microbiology, Hanover, NH
- Characterized the structure and function of human Fc receptors

June, 1988

Ph.D. Biochemistry –
Dartmouth College, Microbiology/Immunology Departments, Hanover, NH (1984-1988)
- Thesis: Cytotoxic trigger molecules on human myeloid cells

June, 1978

B.S. Biology –
Allegheny College, Meadville, PA (1974-1978)

PROFESSIONAL AFFILIATIONS

American Association of Immunologists (AAI)

PUBLICATIONS

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PATENTS
(List limited to published US filings)

US 6,682,928 Cells expressing anti-Fc receptor binding components

US 6,410,690 Therapeutic compounds comprised of anti-Fc receptor antibodies

US 6,395,272 Therapeutic compounds comprised of anti-Fc receptor antibodies

US 6,365,161 Therapeutic compounds comprised of anti-Fc receptor binding agents

US 6,303,755 Therapeutic multispecific compounds comprised of anti-FcA receptor antibodies

US 6,270,765 Therapeutic compounds comprised of anti-Fc receptor antibodies

US 6,193,966 Therapeutic multispecific compounds comprised of anti-Fcα receptor antibodies

US 5,922,845 Therapeutic multispecific compounds comprised of anti-Fcα receptor antibodies

US 5,837,243 Therapeutic compounds comprised of anti-Fc receptor antibodies

US 20040006215 Human monoclonal antibodies against CD30

US 20040005318 Methods of treatment using CTLA-4 antibodies

US 20020032312 Therapeutic compounds comprised of anti-Fc receptor antibodies

US 20010014328 Therapeutic multispecific compounds comprised of anti-Fcα receptor antibodies